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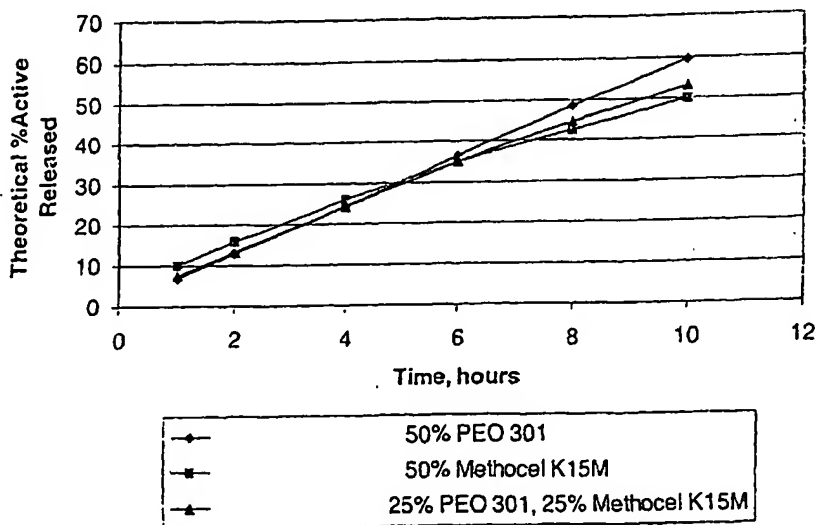
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- (71) Applicant: **DEPOMED, INC.** [US/US]; 1360 O'Brien Drive, Menlo Park, CA 94025-1436 (US).
- (72) Inventors: **DEVANE, John**; Heron Cove, Barrymore, Athlone, County Roscommon (IE). **CUMMING, K. Iain**; 46 Old Cabra Road, Dublin 7 (IE). **HOU, Sui Yuen, Eddie**; 380 Shad Court, Foster City, CA 94404 (US). **GUSLER, Gloria, M.**; 20671 McClellan Road, Cupertino, CA 95014 (US).
- (74) Agent: **SINGH, Sunil, K.**; Cooley Godward LLP, 3000 El Camino Real, Five Palo Alto Square, Palo Alto, CA 94306-2155 (US).
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(54) Title: METHODS OF TREATMENT USING A GASTRIC RETAINED LOSARTAN DOSAGE

Losartan In -Vitro Dissolution



(57) Abstract: A method of treatment for hypertension and other disease states is described, which comprises the delivery of losartan in a gastric retained dosage form.

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METHODS OF TREATMENT USING A GASTRIC RETAINED LOSARTAN
DOSAGE

Background of the Invention

Technical Field

The present invention relates to the use of losartan in a gastric retained dosage form. More specifically, the invention relates to the use of such dosage form to treat hypertension and other disease states.

Background

Losartan was the first orally active angiotensin II receptor antagonist (McIntyre, et al., *Pharmacol. Ther.* 74(2):181-194 (1997); Siegel, *Journal of Hypertension* 11(3):S19-S22 (1993)). At present, losartan is marketed as losartan potassium ($C_{22}H_{22}ClKN_6O$), which is chemically described as 2-butyl-4-chloro-1[p-(o-1H-tetrazol-5-ylphenyl) benzyl]imidazole-5-methanol monopotassium salt. Losartan potassium is administered to treat hypertension and is commercially available in 25 mg, 50 mg and 100 mg tablet dosage forms. Dosage regimens are typically 25 mg to 100 mg either once- or twice-daily.

The effects of losartan potassium are observed at 24 hours for both the 50 mg and the 100 mg dosages, but not for the 25 mg dosage (McIntyre, et al., *supra*). McIntyre also observes that there is an approximately 30% blockade of the diastolic pressure response to angiotensin II at 24 hours after dosing. Further, the peak:trough blood pressure ratio (5-6 hours after dosing: 24 hours after dosing) was found to be 60% for a 50 mg dosage and 72% for a 100 mg dosage.

Although some researchers have noted that once-daily and twice-daily administrations demonstrate equivalent efficacy, Bauer, et al., *Arch. Intern. Med.* 155:1361-1368 (1995) has indicated that a 50 mg twice daily dosing regimen is more effective than a 100 mg once-daily dosing regimen. Since the blood pressure responses tends to closely follow the plasma levels of the active metabolite of losartan potassium, and the t_{max} and half-life of the active metabolite are 2-4 hours and 6-9 hours (4-5 for Japanese patients tested), respectively (Bauer, et al., *supra*), the superiority of the bid dosing is expected.

A controlled release formulation of losartan would have the desirable benefit of eliminating the need for bid dosing. It was hypothesized that a gastric retentive controlled release dosage form may improve the absorption of losartan.

These problems are addressed by the instant invention, which provides for the once-daily delivery of losartan by means of a gastric retained dosage form to treat hypertension. A gastric retained dosage form is particularly beneficial for delivery of losartan due to its prolonged transit in the upper gastrointestinal tract and thus not have the problem of reduced bioavailability.

Summary of the Invention

One aspect of the invention relates to a method of treating hypertension comprising administering a therapeutically effective amount of losartan or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

Yet another aspect of the invention relates to a method of treating heart failure comprising administering a therapeutically effective amount of losartan or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

Still another aspect of the invention relates to an improved method of administering a therapeutically effective amount of losartan to a patient in need thereof, the improvement comprising administering losartan or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form.

Brief Description of the Drawings

Figure 1 illustrates *in-vitro* dissolution of losartan as a function of time.

Description of the Invention

The invention relates to a method of treating a disease state, such as hypertension, by administering losartan in a once-daily gastric retained dosage form. The gastric retained dosage form is particularly beneficial for delivery of losartan due to its prolonged transit in the upper gastrointestinal tract, which allows the drug to be absorbed adequately. In addition, a gastric retained dosage form increases the t_{max} and allows for a smoother, more prolonged anti-hypertensive effect. Furthermore, a gastric retained losartan dosage form

also reduces the C_{max} , which may reduce the incidence of losartan's major side effect, dizziness (McIntyre, et al., *supra*).

Method of Treatment

5 The instant invention is a method of treating a disease state comprising administering a therapeutically effective amount of losartan, or a pharmaceutically acceptable salt thereof, once-daily in a gastric retained dosage form to a mammal in need of such treatment. As used herein, the term "treating" covers treating the specified disease in a mammal, particularly a human, and includes:

- 10 (i) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it;
- (ii) inhibiting the disease, i.e. arresting its development; or
- (iii) relieving the disease, i.e. causing regression of the disease.

15 One embodiment of the invention relates to an improved method of administering a therapeutically effective amount of losartan to a patient in need thereof, the improvement comprising administering losartan or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form.

20 Other embodiments of the invention relate to methods of treating specific disease states comprising administering a therapeutically effective amount of losartan or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment. Such methods find utility in treating numerous disease states that are currently being treated with conventional immediate release formulations of losartan and include, by way of illustration and not limitation, hypertension, congestive heart failure, diabetic nephropathy and myocardial infarction.

25 The invention also contemplates administering one or more additional therapeutic agents with the losartan treatment. The selection of these additional therapeutic agents will depend upon the specific disease state being treated, and are described in detail below.

Active Ingredient

30 The active ingredient in the method of the invention is losartan. Losartan is preferably used in the form of a pharmaceutically acceptable salt that retains the biological effectiveness and properties of losartan and is not biologically or otherwise undesirable. As

used herein, the term "losartan" is intended to include the agent itself, as well as its pharmaceutically acceptable salts.

Pharmaceutically acceptable salts may be amphoteric and may be present in the form of internal salts. Losartan may form acid addition salts and salts with bases.

5 Exemplary acids that can be used to form such salts include, by way of example and not limitation, mineral acids such as hydrochloric, hydrobromic, sulfuric or phosphoric acid or organic acids such as organic sulfonic acids and organic carboxylic acids. Salts formed with inorganic bases include, for example, the sodium, potassium, lithium, ammonium, calcium, and magnesium salts. Salts derived from organic bases include, for example, the
10 salts of primary, secondary and tertiary amines, substituted amines including naturally-occurring substituted amines, and cyclic amines, including isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-dimethyl aminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine,
15 piperidine, N-ethylpiperidine, fumarate, maleate, succinate, acetate and oxalate.

A particularly suitable pharmaceutically acceptable salt is losartan potassium ($C_{22}H_{22}ClKN_6O$), which is chemically described as 2-butyl-4-chloro-1[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt.

Additional Therapeutic Agents

20 The methods of the invention also contemplate the addition of one or more therapeutic agents with the losartan treatment.

For those embodiments of the invention where the losartan gastric retained dosage form is administered to treat hypertension, such additional therapeutic agents can be selected from the group consisting of diuretics, beta-blockers, angiotensin converting
25 ("ACE") inhibitors, calcium channel blockers, alpha-blockers, alpha-beta blockers, vasodilators, alpha antagonists (centrally acting), and adrenergic neuron blockers; and are preferably selected from the group consisting of diuretics, beta-blockers and calcium channel blockers.

For those embodiments of the invention where the losartan gastric retained dosage form is administered to treat congestive heart failure, such additional therapeutic agents can
30 be selected from the group consisting of diuretics, ACE inhibitors, digoxin, vasodilators (direct vasodilators, calcium channel blockers and nitrates), beta blockers, and statins; and

are preferably selected from the group consisting of diuretics, digoxin, direct vasodilators and nitrates.

For those embodiments of the invention where the losartan gastric retained dosage form is administered to treat diabetic nephropathy, such additional therapeutic agents can be diuretics.

For those embodiments of the invention where the losartan gastric retained dosage form is administered to treat myocardial infarction, such additional therapeutic agents can be selected from the group consisting of ACE inhibitors, diuretics, vasodilators, beta blockers, anticoagulants and thrombolytics.

Examples of compounds within each of these classes is set forth below, which is intended to be illustrative and not limiting in any manner

Examples of suitable thiazide diuretics include bendroflumethiazide, chlorothiazide, chlorthalidone, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, metolazone, polythiazide, quinethazone and trichlormethiazide; and are preferably selected from the group consisting of hydrochlorothiazide and chlorothiazide. Examples of suitable loop diuretics include bumetanide, ethacrynic acid and furosemide. Examples of suitable potassium-sparing diuretics include amiloride, spironolactone and triamterene.

Suitable beta-blockers include propranolol, timolol, and metoprolol.

Examples of suitable ACE inhibitors include captopril, enalapril, lisinopril, quinapril, ramipril, benazepril and fosinopril.

Suitable calcium channel blockers include verapamil, diltiazem, nimodipine, nifedipine, nicardipine, felodipine, isradipine and amlodipine.

Exemplary suitable alpha-blockers include prazosin, terazosin, doxazosin, phenoxybenzamine and phentolamine.

Suitable alpha-beta blockers include labetalol.

Examples of suitable vasodilators include, by way of illustration and not limitation, hydralazine, minoxidil, diazoxide and nitroprusside.

Suitable alpha antagonists (centrally acting) include methyl dopa, clonidine, guanabenz and guanfacine.

Examples of suitable adrenergic neuron blockers include guanfacine, guanethidine, guanadrel, and reserpine.

Dosage

In general, the term "therapeutically effective amount" refers to that amount which is sufficient to effect treatment, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending on the subject being treated, the severity of the disease state and the manner of administration, and may be determined
5 routinely by one of ordinary skill in the art.

In particular, for use in the treatment of hypertension or heart failure with a gastric retained dosage form, losartan may be used at doses appropriate for treating hypertension or heart failure with immediate release dosage forms. However, the gastric retained dosage
10 form is designed to provide for bioavailability of losartan at a level greater than or equal to 80% ($\geq 80\%$) relative to an equal dose of an immediate release dosage form. Typically, the method of the invention will involve administering losartan on a once-daily basis for as long as the condition persists.

An effective amount of losartan per dosage for the treatment of hypertension is typically in the range of about 10-150 mg/dosage, typically about 25-100 mg/dosage, more
15 typically about 50-100 mg/dosage.

An effective amount of losartan per dosage for the treatment of congestive heart failure is typically in the range of about 10-150 mg/dosage, typically about 12.5-100 mg/dosage, more typically about 25-100 mg/dosage.

An effective amount of losartan per dosage for the treatment of diabetic nephropathy is typically in the range of about 10-150 mg/dosage, typically about 12.5-100 mg/dosage,
20 more typically about 25-100 mg/dosage.

An effective amount of losartan per dosage for the treatment of myocardial infarction is typically in the range of about 10-150 mg/dosage, typically about 25-100
25 mg/dosage, more typically about 25-50 mg/dosage.

Dosage Regimen

The methods of the invention provide a once-daily dose of the losartan gastric retained dosage form. The dosage can be administered at any time, but it is preferred that the dosage is administered at the same approximate time each day for the duration of
30 treatment. In addition, it is preferred that the gastric retained dosage form be taken with food.

Accordingly, in one embodiment of the invention, losartan is administered once-daily in the morning, for example, upon rising or with the morning meal. In another embodiment, losartan is administered once-daily in the evening (e.g., with the evening meal or near bedtime).

5 In another aspect of the invention, the method of administering a therapeutically effective amount of losartan in a gastric retained dosage form further includes administering one or more additional therapeutic agents.

The additional therapeutic agents can be administered at the same time or at a different time than the administration of losartan, and will depend upon the nature of the disease being treated as well as the agent itself. For example, when the additional agent is a diuretic, a once-daily dose is sufficient and it may be administered at the same time or at a different time than losartan. For purposes of facilitating patient compliance, administration at the same time is preferred.

15 Dosage Form

There are several drug delivery systems that are suitable for use in delivering losartan in the method of the invention as they are particularly tailored to be gastric-retained dosages, such as the swellable bilayer described by Franz, et al., US Patent No. 5,232,704; the multi-layer tablet with a band described by Wong, et al., US Patent No. 6,120,803; the membrane sac and gas generating agent described in Sinnreich, US Patent No. 4,996,058; 20 the swellable, hydrophilic polymer system described in Shell, et al., US Patent No. 5,972,389 and Shell, et al., WO 9855107; all of which are incorporated herein by reference.

Of particular interest are gastric retained dosage forms that contain hydrophilic polymers that swell to a size such that it promotes retention of the dosage form in the fed mode. For example, the gastric retained dosage form can contain polymers with a high swelling capacity such as polyethylene oxide, hydroxyethylcellulose and hydroxypropylmethylcellulose. The polymers are preferably of a moderate to high molecular weight (4×10^3 to greater than 10^7) so that the majority of the losartan can be delivered via a diffusional mechanism, but such that eventually the dosage form dissolved in the gastrointestinal tract. In one embodiment of the invention, the dosage form should 30 swell to approximately 115% of its original volume within one hour after administration, and at a later time should swell to a volume that is 150% or more of the original volume.

Fillers, binders, lubricants and other additives may also be included in the gastric retained dosage form, such as are well known to those of skill in the art.

A typical dosage form would provide for a drug delivery profile such that losartan both on an *in vivo* and *in vitro* basis, is delivered for at least 5 hours, and typically over a time period of about 6-10 hours. Given the conversion of losartan potassium to its more potent metabolite, the anti-hypertensive effect is ideally sustained more evenly over a 24 hour time period, allowing the once-daily dosing to be effective. In order to provide for sustained delivery, it is preferable that at least 40wt% of losartan is retained in the dosage form after 1 hour, i.e., no more than 60wt% of the drug is administered in the first hour. In addition, it may be desired to utilize a dosage form that provides for substantially all of the losartan to be delivered over the intended duration, which is typically about 6-24 hours, where substantially all is taken to mean at least about 85wt% of the losartan is administered.

In one embodiment of the invention, the gastric retained dosage form of losartan is a capsule dosage form that allows for the extended release of losartan in the stomach and comprises: (a) at least one component that expands on contact with gastric juice and contains an agent capable of releasing carbon dioxide or nitrogen, losartan or a pharmaceutically acceptable salt thereof; (b) at least one hydrophilic membrane in the form of a sachet which contains component (a), expands by inflation, floats on the aqueous phase in the stomach and is permeable to gastric juice and; (c) a capsule dosage form which contains components (a) and (b) and which disintegrates without delay in the stomach under the action of gastric juice. Component (a) may also contain a pharmaceutically acceptable hydrophilic swelling agent such as lower alkyl ethers of cellulose, starches, water-soluble aliphatic or cyclic poly-N-vinylamides, polyvinyl alcohols, polyacrylates, polymethacrylates, polyethylene glycols and mixtures thereof, as well as other materials used in the manufacture of pharmaceutical dosage forms. Further details regarding an example of this type of dosage form can be found in Sinnreich, US Patent No. 4,996,058.

In another embodiment of the invention, the gastric retained dosage form of losartan is an extended release oral drug dosage form for releasing losartan into the stomach, duodenum and small intestine of a patient, and comprises: a single or a plurality of solid particles consisting of losartan or a pharmaceutically acceptable salt thereof dispersed within a polymer that (i) swells unrestrained dimensionally by imbibing water from gastric fluid to increase the size of the particles to promote gastric retention in the stomach of the

patient in which the fed mode has been induced; (ii) gradually the losartan diffuses or the polymer erodes over a time period of hours, where the diffusion or erosion commences upon contact with the gastric fluid; and (iii) releases losartan to the stomach, duodenum and small intestine of the patient, as a result of the diffusion or polymeric erosion at a rate corresponding to the time period. Exemplary polymers include polyethylene oxides, alkyl substituted cellulose materials and combinations thereof, for example, high molecular weight polyethylene oxides and high molecular weight or viscosity hydroxypropylmethylcellulose materials. Further details regarding an example of this type of dosage form can be found in Shell, et al., US Patent No. 5,972,389 and Shell, et al., WO 9855107.

In yet another embodiment, a bi-layer tablet releases losartan to the upper gastrointestinal tract from an active containing layer, while the other layer is a buoyant or floating layer. Details of this dosage may be found in Franz, et al., US Patent No. 5,232,704. This dosage form may be surrounded by a band of insoluble material as described by Wong, et al., US Patent No. 6,120,803.

Another embodiment of the invention uses a gastric retained swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose. This dosage form is illustrated in Example 1 and further details may be found in Gusler, et al., "Optimal Polymer Mixtures For Gastric Retentive Tablets," filed on like date herewith and identified as Attorney Docket No. 15662-001700US, the disclosure of which is incorporated herein by reference.

For those embodiments of the invention that include further administering one or more additional therapeutic agents simultaneously with losartan, these agents can either be administered in a gastric retained dosage form that includes losartan or can be administered in a dosage form that is separate from losartan. Exemplary dosage forms are described below.

Dosage Form of Additional Agents

For those embodiments of the invention that include further administering one or more additional therapeutic agents, such dosages can be any suitable formulation as are well known in the art. For those additional agents where controlled release is desirable, the agent may be incorporated in the losartan gastric retained dosage form or be administered in a separate gastric retained or other controlled release formulation dosage form. For those

additional agents where immediate release is desirable, the agent may be incorporated in a coating around the losartan gastric retained dosage form, the agent may be simply enclosed in the capsule of the aforementioned losartan gastric retained capsule dosage form, or the agent may be administered in a separate immediate release dosage form.

5 Typically, dosage forms contain the additional agent (diuretic) in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. Usually the amount of active agent is about 0.1-95wt%, more typically about 1-50wt%. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's
10 Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 18th Edition, 1990. The dosage form to be administered will, in any event, contain a quantity of the additional therapeutic agent(s) in an amount effective to alleviate the symptoms of the subject being treated.

In the preparation of pharmaceutical formulations containing the additional
15 therapeutic agent in the form of dosage units for oral administration the agent may be mixed with solid, powdered ingredients, such as lactose, microcrystalline cellulose, maltodextrin, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol
20 waxes. The mixture is then processed into granules or pressed into tablets such as chewable and oral disintegrating tablets.

Soft gelatin capsules may be prepared by mixing the active agent and vegetable oil, fat, or other suitable vehicle. Hard gelatin capsules may contain granules of the active agent, alone or in combination with solid powdered ingredients such as lactose, saccharose,
25 sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing about 0.2-20wt% of the active agent and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may
30 contain coloring agents, flavoring agents, saccharin and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

When the method of the invention includes administering a diuretic, there are numerous commercially available dosage forms that can be administered, particularly immediate release dosage forms. In addition, other formulations can be readily designed based upon knowledge in the art, and include a coating on the gastric-retained delivery systems described above.

Typical dosage forms of the diuretic suitable for use in the invention include tablets, capsules, oral solutions and oral suspensions. One of skill in the art can readily prepare one of these exemplary formulations or the diuretic can be administered by means of one of the numerous commercially available products, examples of which are provided below.

Commercially available loop diuretics include, for example, Bumex® (bumetanide, Roche Pharmaceuticals), Edecrin® (ethacrynic acid, Merck), Lasix® (furosemide, Hoechst) and Myrosemide (furosemide).

Commercially available potassium-sparing diuretics include, for example, Midamor® (amiloride, Merck), Aldactone® (spironolactone, G. D. Searle) and Dyrenium® (triamterene, Smith Kline).

Commercially available thiazide diuretics include, for example, Naturetin® (bendroflumethiazide, Squibb); Diuril® (chlorothiazide, Merck); Thalitone® (chlorthalidone, Boehringer); Microzide®, HydroDIURIL® and Oretic® (hydrochlorothiazide, Watson, Merck and Abbott, respectively); Saluron® and Diucardin® (hydroflumethiazide, Bristol-Myers and American Home Products, respectively); Enduron® (methyclothiazide, Abbott); Mykrox® and Zaroxolyn® (metolazone, Fisons); Renese® (polythiazide, Pfizer); Hydromox® (quinethazone, American Cyanamid); and Naqua® (trichlormethiazide, Schering).

Although specific examples of suitable diuretic formulations are described above, it is understood that the invention is not limited to those examples as there are numerous other formulations that can be used to deliver the diuretic.

The general methods of the invention are best understood with reference to the following examples which are intended to enable those skilled in the art to more clearly understand and to practice the present invention. These examples are not intended, nor are they to be construed, as limiting the scope of the invention, but are merely illustrative and representative thereof.

Example 1

Tablets were manufactured using a dry blend process, and hand-made on a Carver 'Auto C' Press (Fred Carver, Inc., Indiana). The dry blend process consisted of blending all of the ingredients in a container, and compressing into a 600-mg tablet using a 0.6299" X 0.3937" Mod Oval die (Natoli Engineering). The parameters for the operation of the Carver Auto 'C' press were as follows: ~2000-2500 lbs. force, 0 second dwell time (the setting on the Carver press), and 100% pump speed.

TABLE 1

Lot #	Formulation Composition (70 w/w)				
	Active	PEO	K15M	LMH	M.St.
A	8.3	50.0	0.0	40.7	1
B	8.3	25.0	25.0	40.7	1
C	8.3	0.0	50.0	40.7	1

Active = Losartan Potassium

PEO = poly(ethylene oxide), grade PolyOx 301, NF FP grade, manufactured by Union Carbide/Dow Chemical Company

K15M = hydroxypropyl methyl cellulose, grade Methocel K15M, premium, manufactured by Dow Chemical Company

LMH = lactose monohydrate, NF, spray-dried, type Fast Flo 316, manufactured by Foremost Farms

M. St. = magnesium stearate, NF, supplied by Spectrum Chemical Company

Example 2

An *in vitro* cumulative release profile was generated, based upon a theoretical percent active added to the formulations of Example 1. The data are presented in Table 2, and Fig. 1.

TABLE 2

Time (hours)	Theoretical wt% of Active Released (Dissolution)		
	A	B	C
1	6.9	7.4	9.9
2	12.8	13.4	15.9
4	24.3	24.3	26.1
6	38.4	35.0	34.8
8	48.6	44.5	42.5
10	59.8	53.4	49.9

Example 3

The following two formulations were manufactured by the dry blend process according to the formulations listed below in Table 3. Losartan potassium was geometrically blended with the remaining excipients by successively blending the losartan potassium with approximately equal quantities of a blend of the remaining excipients until all of the excipients were blended together with the active ingredient. After geometrically blending the losartan potassium, the tablets were compressed at 2500 pounds of force using a 0.3937" X 0.6299" modified oval die (Natoli Engineering, St. Charles, MO) using a Carver Autopress (Fred Carver, Inc., Wabash, IN) with a pharmaceutical die holder. For bi-layer tablets (GR-1) the active layer was placed in the die, tamped lightly, and then filled with the non-active layer. The release of the active component, losartan potassium, is illustrated in Table 4 and is based on the percentage active in the formulation.

15

Table 3: Summary of Prototypes (50-mg Losartan Potassium per tablet)			
Excipients or Active	GR-1		GR-2
	Active Layer	Non-Active Layer	
Losartan Potassium	16.65%	-	8.29%
Hydroxypropyl Methylcellulose (Methocel® K4M Premium, USP)	-	-	25.01%
Hydroxypropyl Methylcellulose (Methocel® K15M Premium, USP)	24.98%	-	-
Hydroxypropyl Methylcellulose (Methocel® K100M Premium, USP)	-	19.02%	-
Polyethylene Oxide (Sentry® PolyOx® WSR 301, NF FP)	24.05%	-	24.99%
(Sentry® PolyOx® WSR 303, NF FP)	-	64.82%	-
Lactose Monohydrate (316 Fast Flo®, NF)	33.36%	-	40.68%
Barium Sulfate, USP/NF	-	15.07%	-
Magnesium Stearate, NF/FCC (Mallinckrodt code 2255)	0.96%	1.10%	1.02%
Mass (mg)	300	300	600
Total Tablet Mass (mg)	600		600

Potassium Losartan was obtained from Gyma Laboratories (Westbury, NY). Methocel® brand hydroxypropyl methylcellulose (also known as hypromellose), USP type 2208, and Sentry® PolyOx® brand polyethylene oxide were obtained from Dow Chemical (Midland, MI). FastFlo® 316, NF brand of lactose monohydrate was obtained from Foremost Farms (Baraboo, WI). Barium sulfate was supplied by Spectrum Quality Products (New Brunswick, NJ) and magnesium stearate was obtained from Mallinckrodt

(Hazelwood, MO). The viscosity of the various types of Methocel® brand hydroxypropyl methylcellulose are 4000 cps, 15,000 cps, and 100,000 cps as a 2% aqueous solution at 20 °C for Methocel® K4M, Methocel® K15M, and Methocel® K100M, respectively. The corresponding number-average molecular weights for Methocel® K4M, Methocel® K15M, and Methocel® K100M are on the order of 80,000, 100,000 and 300,000-350,000, respectively. Sentry® PolyOx® WSR 301, NF FP and Sentry® PolyOx® WSR 303, NF FP have viscosity-average molecular weights of approximately 4,000,000 and 7,000,000, respectively.

Table 4: In-vitro Release for Tablets of Example 3

Time Point	%Active Released	
	GR-1	GR-2
1 hr	10.69	9.39
2 hr	25.90	20.50
4 hr	56.85	44.01
6 hr	86.97	68.09
8 hr	95.54	88.94

Example 4

The formulations manufactured in Example 3, with the addition of a radio-opaque string crossed in the center like an "X" in the single layer tablet (GR-2) and in the active layer of the bi-layer tablet (GR-1), were administered to five beagle dogs in a non-randomized pharmacokinetic study with concurrent C-arm fluoroscopy to determine gastric retention. This study used five adult female beagle dogs, weighing approximately 7-9 kg. The dogs were fasted overnight (at least 14 hr) and were then fed a 50-gm meal (a mixture of 50% dry and 50% canned dog food). The immediate release (IR) comparator (Cozaar®, 50 mg tablet, manufactured by Merck & Co.) or one of the GR formulations (GR-1 or GR-2) containing radio-opaque strings was dosed fifteen minutes after the food had been consumed by the dogs. The dosing was done in a non-randomized manner. There was a washout period of at least 6 days between dosing.

The study concurrently determined the pharmacokinetic profile and the gastric retention. The gastric retention was determined by using C-arm fluoroscopy. An image

was taken every 30 minutes until either the GR system had emptied from the stomach or it had completely eroded in the stomach. The erosion was determined by the separation of the two strings. Barium sulfate allowed visualization of the swelling layer as well. The pharmacokinetic (PK) analysis was achieved by drawing 3 mL blood samples through venipuncture from either the cephalic or jugular veins. The samples were taken at pre-dosing and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hrs post dosing.

The pharmacokinetic parameters and the gastric retention for are shown in Table 5 below. One dog failed to complete the IR leg. The gastric retention time (GR Time) was the time that the dosage form left the stomach or completely eroded which ever was shorter, as observed using the C-arm fluoroscopy.

Table 5: Losartan Potassium Pharmacokinetic Parameters						
Pharmacokinetic Parameter		IR (N=4)	GR-1 (N=5)	GR-2 (N=5)	Relative to the IR	
					GR-1 (N=4)	GR-2 (N=4)
AUC (ng/mL.h)	Mean	486	590	461	122%	94%
	Std Dev	133	202	176	29%	24%
C _{max} (ng/mL)	Mean	224	105	72	48%	32%
	Std Dev	58.5	31.7	24.1	15%	8%
t _{max} (hr)	Mean	0.88	2.50	5.25	n/a	n/a
	Std Dev	0.25	0.58	0.50	n/a	n/a
GR Time (hr)	Mean	n/a	7.6	6.8	n/a	n/a
	Std Dev	n/a	2.5	0.5	n/a	n/a

As shown in Table 5 above both formulations demonstrated good gastric retention with acceptable bioavailability when compared to the immediate release tablet. The maximum plasma concentration was reduced and the time to maximum plasma was increased as expected for a sustained release product.

Each of the patent applications, patents, publications, and other published documents mentioned or referred to in this specification is herein incorporated by reference in its entirety, to the same extent as if each individual patent application, patent, publication, and other published document was specifically and individually indicated to be incorporated by reference.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

What is claimed is:

1. A method of treating hypertension comprising administering a therapeutically effective amount of losartan or a pharmaceutically acceptable salt thereof, in a gastric retentive dosage form to a mammal in need of such treatment.
2. The method of Claim 1 wherein the dosage form is administered once-daily.
3. The method of Claim 2 wherein the dosage form is administered with a meal.
4. The method of Claim 1 which further comprises administering one or more therapeutic agents selected from the group consisting of diuretics, beta-blockers, ACE inhibitors, calcium channel blockers, alpha-blockers, alpha-beta blockers, vasodilators, alpha antagonists (centrally acting), and adrenergic neuron blockers.
5. The method of Claim 1 wherein the amount of losartan in the dosage form is about 10-150 mg.
6. The method of Claim 5 wherein the amount of losartan in the dosage form is about 25-100 mg.
7. The method of Claim 6 wherein the amount of losartan in the dosage form is about 50-100 mg.
8. The method of Claim 1 wherein the dosage form is an extended release oral drug dosage form for releasing losartan into the stomach, duodenum and small intestine of the mammal.
9. The method of Claim 8 wherein losartan is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the losartan is retained in the dosage form after 1 hour.
10. The method of Claim 9 wherein the dosage form provides administration of at least 85wt% of the losartan over a period of about 6-24 hours.
11. The method of Claim 9 wherein the dosage form contains a hydrophilic polymer that swells to a size such that the dosage form is retained in the stomach in the fed mode.

12. The method of Claim 11 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.
13. The method of Claim 9 wherein the dosage form further comprises a gas generating agent.
14. The method of Claim 13 wherein losartan is contained in a membrane sachet with the gas generating agent.
15. The method of Claim 1 wherein the dosage form is an adhesive tablet.
16. The method of Claim 1 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of losartan in the stomach.
17. The method of Claim 1 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.
18. A method of treating heart failure comprising administering a therapeutically effective amount of losartan or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.
19. The method of Claim 18 wherein the dosage form is administered once-daily.
20. The method of Claim 19 wherein the dosage form is administered with a meal.
21. The method of Claim 18 which further comprises administering one or more therapeutic agents selected from the group consisting of diuretics, ACE inhibitors, digoxin, and vasodilators selected from the group consisting of direct vasodilators, calcium channel blockers and nitrates.
22. The method of Claim 18 wherein the amount of losartan in the dosage form is about 10-150 mg.
23. The method of Claim 22 wherein the amount of losartan in the dosage form is about 12.5-100 mg.
24. The method of Claim 23 wherein the amount of losartan in the dosage form is about 25-100 mg.

25. The method of Claim 18 wherein the dosage form is an extended release oral drug dosage form for releasing losartan into the stomach, duodenum and small intestine of the mammal.
26. The method of Claim 25 wherein losartan is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the losartan is retained in the dosage form after 1 hour.
27. The method of Claim 26 wherein the dosage form provides administration of at least 85wt% of the losartan over a period of about 6-24 hours.
28. The method of Claim 26 wherein the dosage form contains a hydrophilic polymer that swells to a size such that the dosage form is retained in the fed mode.
29. The method of Claim 28 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.
30. The method of Claim 26 wherein the dosage form further comprises a gas generating agent.
31. The method of Claim 30 wherein losartan is contained in a membrane sachet with the gas generating agent.
32. The method of Claim 18 wherein the dosage form is an adhesive tablet.
33. The method of Claim 18 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of losartan in the stomach.
34. The method of Claim 18 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.
35. A method of treating diabetic nephropathy comprising administering a therapeutically effective amount of losartan or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.
36. The method of Claim 35 wherein the dosage form is administered once-daily.
37. The method of Claim 36 wherein the dosage form is administered with a meal.

38. The method of Claim 35 which further comprises administering one or more therapeutic agents selected from the group consisting of ACE inhibitors, calcium channel blockers, diuretics, and beta blockers.
39. The method of Claim 35 wherein the amount of losartan in the dosage form is about 10-150 mg.
40. The method of Claim 39 wherein the amount of losartan in the dosage form is about 25-100 mg.
41. The method of Claim 40 wherein the amount of losartan in the dosage is form about 50-100 mg.
42. The method of Claim 35 wherein the dosage form is an extended release oral drug dosage form for releasing losartan into the stomach, duodenum and small intestine of the mammal.
43. The method of Claim 42 wherein losartan is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the losartan is retained in the dosage form after 1 hour.
44. The method of Claim 43 wherein the dosage form provides administration of at least 85wt% of the losartan over a period of about 6-24 hours.
45. The method of Claim 43 wherein the dosage form contains a hydrophilic polymer that swells to a size such that the dosage form is retained in the fed mode.
46. The method of Claim 45 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.
47. The method of Claim 43 wherein the dosage form further comprises a gas generating agent.
48. The method of Claim 47 wherein losartan is contained in a membrane sachet with the gas generating agent.
49. The method of Claim 35 wherein the dosage form is an adhesive tablet.
50. The method of Claim 35 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of losartan in the stomach.

51. The method of Claim 35 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.
52. A method of treating myocardial infarction comprising administering a
5 therapeutically effective amount of losartan or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.
53. The method of Claim 52 wherein the dosage form is administered once-daily.
54. The method of Claim 53 wherein the dosage form is administered with a meal.
55. The method of Claim 52 which further comprises administering one or more
10 therapeutic agents selected from the group consisting of thrombolytics, beta blockers, diuretics, ACE inhibitors, calcium channel blockers, anticoagulants, and nitrates.
56. The method of Claim 52 wherein the amount of losartan in the dosage form is about 10-150 mg.
- 15 57. The method of Claim 56 wherein the amount of losartan in the dosage form is about 12.5-100 mg.
58. The method of Claim 57 wherein the amount of losartan in the dosage form is about 25-50 mg.
59. The method of Claim 52 wherein the dosage form is an extended release oral drug
20 dosage form for releasing losartan into the stomach, duodenum and small intestine of the mammal.
60. The method of Claim 59 wherein losartan is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the losartan is retained in the dosage form after 1 hour.
- 25 61. The method of Claim 60 wherein the dosage form provides administration of at least 85wt% of the losartan over a period of about 6-24 hours.
62. The method of Claim 60 wherein the dosage form contains a hydrophilic polymer that swells to a size such that the dosage form is retained in the fed mode.

63. The method of Claim 62 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.
- 5 64. The method of Claim 60 wherein the dosage form further comprises a gas generating agent.
65. The method of Claim 64 wherein losartan is contained in a membrane sachet with the gas generating agent.
66. The method of Claim 52 wherein the dosage form is an adhesive tablet.
67. The method of Claim 52 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of losartan in the stomach.
- 10 68. The method of Claim 52 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.
69. An improved method of administering a therapeutically effective amount of losartan to a patient in need thereof, the improvement comprising administering losartan or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form.
- 15 70. The method of Claim 69 wherein the dosage form is administered once-daily.
71. The method of Claim 70 wherein the dosage form is administered with a meal.
72. The method of Claim 69 where the patient is being treated for hypertension.
- 20 73. The method of Claim 69 where the patient is being treated for heart failure.
74. The method of Claim 69 where the patient is being treated for diabetic nephropathy.
75. The method of Claim 69 where the patient is being treated for myocardial infarction.
76. The method of Claim 69 wherein the dosage form is an extended release oral drug dosage form for releasing losartan into the stomach, duodenum and small intestine of the mammal.
- 25 77. The method of Claim 76 wherein losartan is administered from the dosage form for a period of at least 5 hours and at least 40wt% of the losartan is retained in the dosage form after 1 hour.

78. The method of Claim 77 wherein the dosage form provides administration of at least 85wt% of the losartan over a period of about 6-24 hours.
79. The method of Claim 77 wherein the dosage form contains a hydrophilic polymer that swells to a size such that the dosage form is retained in the fed mode.
- 5 80. The method of Claim 79 wherein the polymer is selected from the group consisting of polyethylene oxides, alkyl substituted cellulose materials, and combinations thereof.
81. The method of Claim 77 wherein the dosage form further comprises a gas generating agent.
- 10 82. The method of Claim 81 wherein losartan is contained in a membrane sachet with the gas generating agent.
83. The method of Claim 69 wherein the dosage form is an adhesive tablet.
84. The method of Claim 69 wherein the dosage form is a film coated dosage form or a capsule dosage form that allows for the extended release of losartan in the stomach.
- 15 85. The method of Claim 69 wherein the dosage form is a swellable, sustained-release tablet having a matrix comprised of poly(ethylene oxide) and hydroxypropylmethylcellulose.

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Losartan In -Vitro Dissolution

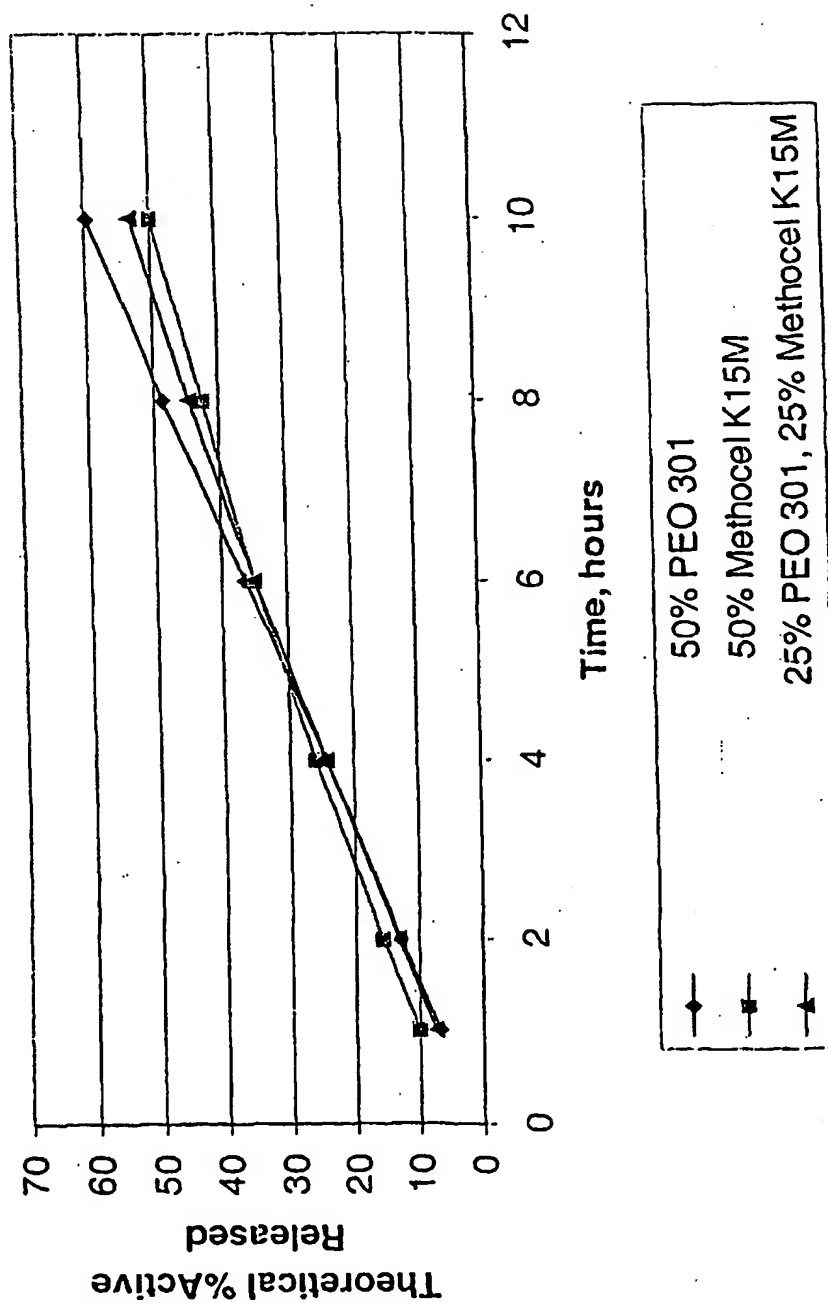


FIG. 1

INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/IB 02/05438

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/20 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 49392 A (MERCK & CO INC ;SWEET CHARLES S (US); CHEN TZYU SHOW H (US); GROSS) 31 December 1997 (1997-12-31)</p> <p>page 5, line 27 -page 6, line 33 page 7, line 18 -page 15, line 26 --- -/--</p>	<p>1-13,16, 18-29, 33, 35-46, 50, 52-63, 67, 69-80,84</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *g* document member of the same patent family

Date of the actual completion of the international search

6 March 2003

Date of mailing of the international search report

14/03/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Muller, S

INTERNATIONAL SEARCH REPORT

Internat pplication No
PCT/IB 02/05438

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 97 02032 A (MERCK & CO INC ;MERCK SHARP & DOHME CHIBRET SN (FR); REMUZZI GIUSE) 23 January 1997 (1997-01-23)</p> <p>page 9, line 5 - line 11 page 9, line 28 -page 11, line 26 ----</p>	<p>1-13,16, 18-29, 33, 35-46, 50, 52-63, 67, 69-80,84</p>
X	<p>WO 01 76573 A (NOVARTIS ERFINDUNGEN ;NOVARTIS AG (CH); GASPARO MARC DE (CH); GRAV) 18 October 2001 (2001-10-18)</p> <p>page 3, line 19 -page 4, line 11 page 13 -page 14; example 1 ----</p>	<p>1-13,16, 18-29, 33, 35-46, 50, 52-63, 67, 69-80,84</p>
X	<p>WO 97 21436 A (MERCK & CO INC ;COHEN SHEILA M (US); WERRMANN JEFFREY G (US)) 19 June 1997 (1997-06-19)</p> <p>page 4, line 24 -page 5, line 6 page 18, line 7 - line 28 claim 5 -----</p>	<p>1-13,16, 18-29, 33, 35-46, 50, 52-63, 67, 69-80,84</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 02/05438

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-85 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat Application No

PCT/18 02/05438

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